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A Pilot Study of Associations Between the Occurrence of Palpitations and Cytokine Gene Variations in Women Prior to Breast Cancer Surgery

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Abstract

Objectives: Palpitations are common and have a negative impact on women's quality of life. While evidence suggests that inflammatory mechanisms may play a role in the development of palpitations, no studies have evaluated for this association in patients with breast cancer who report palpitations prior to surgery. The purpose of this pilot study was to evaluate for associations between the occurrence of palpitations and single nucleotide polymorphisms (SNPs) in genes for pro- and anti-inflammatory cytokines, their receptors, and transcriptional regulators.

Methods: Patients were recruited prior to surgery and completed a self-report questionnaire on the occurrence of palpitations. Genotyping of SNPs in cytokine genes was performed using a custom array. Multiple logistic regression analyses were done to identify associations between the occurrence of palpitations and SNPs in fifteen candidate genes.

Results: Of the 82 SNPs evaluated in the bivariate analyses, eleven SNPs in 6 genes were associated with the occurrence of palpitations. After controlling for functional status, the occurrence of back pain, and self-reported and genomic estimates of race/ethnicity, 3 SNPs in 3 different genes (i.e., interleukin (IL) 1-beta (IL1B) rs1143643, IL10 rs3024505, IL13 rs1295686) were associated with the occurrence of palpitations prior to surgery (all $p \leq .038$).

Conclusions: While these preliminary findings warrant replication, they suggest that inflammatory mechanisms may contribute to the subjective sensation of palpitations in women prior to breast cancer surgery.

Keywords

breast cancer, cardio-oncology, cytokines, interleukins, menopausal symptoms, palpitations, single nucleotide polymorphisms

Introduction

Women with breast cancer experience menopausal symptoms associated with natural menopause and aging; with the withdrawal of hormone therapy at the time of diagnosis; and/or with the receipt of anti-estrogen treatment (Marino et al., 2014; Moon et al., 2017). In these patients, one relatively common, but understudied menopausal symptom is palpitations (Sheng et al., 2022). This symptom is captured as feelings of missed, irregular, rapid, or exaggerated heartbeats (Sheng et al., 2021). In the general population, palpitations affect 20% to 42% of peri-menopausal and 16% to 54% of post-menopausal women (Carpenter et al., 2021).

Only 3 studies have evaluated for palpitations in women with breast cancer (Choo et al., 2019; Kyvernitakis et al., 2014; Sheng et al., 2022). In the first 2 studies that evaluated patients on oral endocrine therapy, the prevalence of palpitations varied based on the duration of treatment (i.e., 48%

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after 12 months (Kyvernitakis et al., 2014); 17.7% after 16 months (Choo et al., 2019); 44% after 24 months (Kyvernitakis et al., 2014). In our recent study that evaluated patients prior to breast cancer surgery, 15.1% of the women reported the occurrence of palpitations (Sheng et al., 2022).

Progress in the treatments for cancer and cardiovascular disease has resulted in a growing population of patients with both chronic conditions. In fact, cardiovascular disease is the second most common cause of morbidity and mortality in oncology patients following recurrence of cancer (Essa & Lip, 2021; Essa & Lip, 2021). With the emergence of the specialty of cardio-oncology, a number of reviews have summarized the common causes of palpitations in oncology patients (Ala et al., 2019; Bansal et al., 2019; Essa & Lip, 2021; Essa et al., 2021). Similar to the general population, common causes of palpitations include: various types of cardiac arrhythmias (e.g., atrial fibrillation, sinus tachycardia, supraventricular tachycardia); anxiety disorders (e.g., generalized anxiety disorder, panic attacks); miscellaneous causes (e.g., caffeine, alcohol, thyroid disorders, electrolyte imbalances); and cancer-specific causes (e.g., chemotherapy, cardiac myomas). Less is known about the potential molecular mechanisms that underlie the occurrence of palpitations in the general population or in women with breast cancer.

One potential mechanism that may underlie the occurrence of palpitations is alterations in inflammatory processes. Several lines of evidence support this hypothesis. First, the cancer itself (Hong et al., 2021; Scheff & Saloman, 2021), as well as the stress associated with the diagnosis (Scheff & Saloman, 2021), result in increases in inflammatory mediators. In addition, other common symptoms in oncology patients are associated with variations in pro- and anti-inflammatory genes and/or perturbations in inflammatory pathways (e.g., fatigue (Kober et al., 2016; Wright et al., 2017), sleep disturbance (Miaskowski et al., 2012b), depression (Saad et al., 2014), and pain (Miaskowski et al., 2019)). Given that one of the etiologies for palpitations is anxiety, findings from our previous study (Miaskowski et al., 2016), that documented relationships between higher levels of anxiety and cytokine gene polymorphisms, supports an examination of these same genes for an association with the occurrence of palpitations. In addition, emerging evidence suggests that inflammation plays a role in cardiovascular disease (Barcena et al., 2022; Silveira Rossi et al., 2022). Finally, evidence from the COVID-19 pandemic suggests that inflammatory processes are involved in the development and maintenance palpitations (Elseidy et al., 2022; Guzik et al., 2020; Khalid et al., 2021; Tajbakhsh et al., 2021).

This analysis extends the findings from our previous study on the occurrence of palpitations, as well as differences in demographic, clinical, and symptom characteristics in women who did and did not report palpitations prior to breast cancer surgery (Sheng et al., 2022). In the current pilot study, we evaluated for associations between the occurrence of palpitations and single nucleotide polymorphisms (SNPs) in cytokine genes and their receptors and regulators.

Methods

Patients and Settings

This exploratory genomic analysis draws its data from a larger, longitudinal study that evaluated neuropathic pain and lymphedema in women following breast cancer surgery. Details of the parent study's methods are published elsewhere (Miaskowski et al., 2012a). Patients were recruited from breast care centers located in a Comprehensive Cancer Center, 2 public hospitals, and 4 community practices. Inclusion criteria were: women who were ≥18 years; scheduled for unilateral breast cancer surgery; able to read, write, and speak English; agreed to participate; and provided written informed consent. Exclusion criteria were: scheduled for bilateral breast cancer surgery or distant metastasis at the time of diagnosis. A total of 516 patients were approached; 410 were enrolled (response rate 79.5%); 398 completed the enrollment assessment; and 310 provided a blood sample for genetic analysis. Commonly cited reasons for refusal to participate were: too busy; overwhelmed with the diagnosis; or insufficient time to complete enrollment assessment prior to surgery.

Instruments

Patients completed self-report questionnaires that provided information on demographic and clinical characteristics. Comorbidity burden was assessed using the Self-Administered Comorbidity Questionnaire (SCQ; Brunner et al., 2008; Sangha et al., 2003). Functional status was evaluated using the Karnofsky Performance Status (KPS) scale (Karnofsky et al., 1948). Medical records were reviewed for disease and treatment information.

Occurrence of palpitations was assessed using a single item from the Menopausal Symptoms Scale (MSS), which was modified from the Seattle Women's Health Study questionnaire (Woods et al., 1999). Women were asked to indicate if they felt their "heart races/pounds" in the past week. This single-item self-report measure is comparable to the way palpitations were measured in previous studies of women with (Choo et al., 2019; Kyvernitakis et al., 2014) and in over 100 studies of women without breast cancer (Sheng et al., 2021).

Study Procedures

Study was approved by the Committee on Human Research at the University of California, San Francisco and the Institutional Review Boards at each study site. During the patient's preoperative visit, a clinician explained the study to the patient and determined her willingness to participate. For those women who were willing to participate, the clinician introduced the patient to the research nurse who determine eligibility and obtained written informed consent. After obtaining informed consent,

patients completed the enrollment questionnaire and provided a blood sample an average of 4 days prior to surgery.

Candidate Gene Selection and Genotyping

Gene selection – Pro-inflammatory genes evaluated in this study were as follows: chemokine (C-C-C motif) ligand 8 (*CXCL8*, previous gene symbol interleukin 8 (*IL8*)), interferon gamma (*IFNG*), *IFNG* receptor 1 (*IFNGR1*), IL1 receptor 1 (*IL1R1*), *IL2*, *IL17A*, and members of the tumor necrosis factor (TNF) family (i.e., lymphotoxin alpha (*LTA*), *TNF*). The anti-inflammatory genes were as follows: *IL1R2*, *IL4*, and *IL10*. In addition, *IFNG1*, *IL1B*, *IL6,* and *IL13* that possess pro- and anti-inflammatory functions and nuclear factor kappa beta 1 (*NFKB1*) and *NFKB2* that regulate transcription of cytokine genes were evaluated (Seruga et al., 2008). Genes were identified and matched with the appropriate symbol stored in the Human Genome Organization (HUGO) Gene Nomenclature Committee (HGNC) database (http://www.genenames.org).

Genotyping procedure - Genomic DNA was extracted from peripheral blood mononuclear cells using the PUREGene DNA Isolation System (Invitrogen, Carlsbad, CA). DNA was quantitated with a Nanodrop Spectrophotometer (ND-1000) and normalized to a concentration of 50 nanograms/microliter (ng/μL; diluted in 10 mM Tris/1 mM EDTA). Genotyping was performed blinded to clinical status and positive and negative controls were included. Samples were genotyped using the Golden Gate genotyping platform (Illumina, San Diego, CA) and processed according to the standard protocol using GenomeStudio (Illumina, San Diego, CA). Signal intensity profiles and resulting genotype calls for each SNP were visually inspected by 2 blinded reviewers. Disagreements were adjudicated by a third reviewer.

SNP selection - Combination of tagging SNPs and literature driven SNPs were selected for analysis. Tagging SNPs were required to be common (defined as having a minor allele frequency of ≥ .05) in public databases (e.g., HapMap). In order to ensure robust genetic association analyses, quality control filtering of SNPs was performed. SNPs with call rates of <95% or a Hardy-Weinberg *p*-value of <.001 were excluded.

As shown in Supplementary Table 1, 82 SNPs from a total of 104 SNPs among 15 candidate genes passed all of the quality control filters and were included in the genetic association analyses. Localization of SNPs on the human genome was performed using the GRCh38 human reference assembly. Regional annotations were identified using the University of California Santa Cruz Human Genome Browser NCBI36/hg18 (http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg18). Potential regulatory involvement of SNPs was investigated using a number of ENCODE data tracks (Encode Project Consortium, 2012). Linkage disequilibrium (LD) between SNPs was calculated with Plink v1.90b4.6 (Chang et al., 2015) using 1000 Genomes Phase 3 release v20130502 variants culled from all populations (Genomes Project Consortium et al., 2010).

Statistical Analyses for Genetic Data

Allele and genotype frequencies were determined by gene counting. Hardy-Weinberg equilibrium was assessed by Chi square or Fisher Exact tests. For the haplotype determinations, measures of LD (i.e., D′ and r^2) were computed from the patients' genotypes with Haploview 4.2. LD-based haplotype block definition was based on D′ confidence interval (Gabriel et al., 2002).

For SNPs that were members of the same haploblock, haplotype analyses were conducted in order to localize the association signal within each gene and to determine if haplotypes improved the strength of the association with the phenotype. Haplotypes were constructed using the program PHASE version 2.1 (Stephens et al., 2001). In order to improve the stability of haplotype inference, the haplotype construction procedure was repeated 5 times using different seed numbers with each cycle. Only haplotypes that were inferred with probability estimates of ≥.85, across the 5 iterations, were retained for downstream analyses. Haplotypes were evaluated assuming a dosage model (i.e., analogous to the additive model).

Ancestry informative markers (AIMs) were used to minimize confounding due to population substructure (Halder et al., 2008). Homogeneity in ancestry among patients was verified by principal component analysis (Price et al., 2006), using Helix Tree (Golden Helix, Bozeman, MT). Briefly, the number of principal components (PCs) was sought that distinguished the major racial/ethnic groups in the sample by visual inspection of scatter plots of orthogonal PCs (i.e., PC 1 versus PC2, PC2 versus PC3). This procedure was repeated until no discernible clustering of patients by their self-reported race/ethnicity was possible (data not shown). One hundred and 6 AIMs were included in the analyses. The first 3 PCs were selected to adjust for potential confounding due to population substructure by including the 3 covariates in all of the logistic regression models.

For association tests, 3 genetic models were assessed for each SNP (i.e., additive, dominant, recessive) using Chi square or Fisher's exact tests. For the significant SNPs, the genetic model that best fit the data, by maximizing the significance of the *p*-value was selected for that SNP. Logistic regression analysis, that controlled for significant covariates, as well as genomic estimates of and self-reported race/ethnicity, was used to evaluate the association between each genotype and occurrence of palpitations. Backwards stepwise approach was used to create the most parsimonious model. Except for genomic

estimates of and self-reported race/ethnicity, only predictors with a p-value of <.05 were retained in the final model. Genetic model fit and both unadjusted and covariate-adjusted odds ratios were estimated using STATA Version 15 (StataCorp, 2017).

Results

Demographics and Clinical Characteristics

A detailed description of the differences in demographic and clinical characteristics between patients with and without palpitations was published previously (Sheng et al., 2022; Supplemental Table 2). Of the 398 patients in this study, 15% reported palpitations. Patients with palpitations had lower annual household income, lower functional status, higher comorbidity burden, and were more likely to self-report back pain.

Candidate Gene Analyses for Palpitations

As summarized in Table 1, genotype frequencies were significantly different between the palpitations groups for nine SNPs and 2 haplotypes spanning 6 genes (IL1B: 2 SNPs; IL10: 1 SNP; IL13: 1 SNP and 2 haplotypes; NFKB1: 3 SNPs; NFKB2: 1 SNP; TNFSF: 1 SNP).

Regression Analyses for Significant Genotypes and Palpitations

To better estimate the magnitude (i.e., odds ratio [OR]) and precision (i.e., confidence interval (CI)) of genotype on the occurrence of palpitations, multivariate logistic regression models were fit. In these regression analyses that included self-reported and genomic estimates of race/ethnicity, the only phenotypic characteristics that remained significant in the multivariable model were functional status (KPS score in 10 unit increments) and the occurrence of back pain (Table 2).

Three SNPs spanning 3 different genes remained significant in the multivariate logistic regression analyses (Table 3, Figures 1(a)-1(c)). For IL1B rs1143643 (G>A), a dominant model fit the data best. Carrying one or 2 doses of the rare A allele (GG vs. GA+AA) was associated with a 2.32-fold increase in the odds of belonging to the palpitations group. For IL10 rs3024505 (C>T), an additive model fit the data best.

Table 1. Summary of Single Nucleotide Polymorphisms Analyzed for Pro- and Anti-Inflammatory Cytokine Genes That Demonstrated Significant Bivariate Associations With the Occurrence of Palpitations Prior to Breast Cancer Surgery.

Gene	SNP	Position	Chr	MAF	Alleles	Chi Square	p-value	Model
IL1B	rs1143643	106042929	2	.383	G>A	FE	0.034	D
IL1B	rs1143633	106045094	2	.392	G>A	FE	0.049	D
IL10	rs3024505	177,638,230	1	.129	C>T	8.092	0.017	A
IL13	rs1295686	127,188,147	5	.265	G>A	FE	0.004	D
IL13	HapA1					8.880	0.012	
IL13	HapA4					6.100	0.047	
NFKB1	rs230494	103706005	4	.434	A>G	FE	0.047	D
NFKB1	rs3774956	103727564	4	.435	C>T	FE	0.031	D
NFKB1	rs1609798	103756488	4	.337	C>T	FE	0.040	D
NFKB2	rs1056890	104152760	10	.305	C>T	10.492	0.005	A
TNFSF	rs2229094	31540556	6	.278	T>C	6.344	0.042	A

Abbreviations. A = additive model, Chr = chromosome, D = dominant model, FE = Fisher's exact test, Hap = haplotype, IL = interleukin, MAF = minor allele frequency, NFKB = nuclear factor kappa beta, SNP= single nucleotide polymorphism, TNFSF = tumor necrosis factor super family.

Table 2. Final Multiple Logistic Regression Model for Significant Covariates Associated With the Occurrence of Palpitations in Women Prior to Breast Cancer Surgery (n = 301).

Predictor	Adjusted odds ratio	Standard error	95% CI	Z	p-value
Self-reported race/ethnicity					
White vs Black	1.35	1.99	0.08, 24.20	0.20	.839
White vs Asian/Pacific Islander	2.08	2.70	0.16, 26.39	0.57	.572
White vs Hispanic/mixed/other	0.27	0.26	0.04, 1.75	- 1.37	.170
KPS score	0.97	0.01	0.94, 0.99	- 2.25	.024
Occurrence of back pain	2.12	0.77	1.04, 4.30	2.07	.039
Overall model fit: X^2 = 20.14; p = .0098; pseudo R^2 = .0772					

Abbreviations. CI = confidence interval; KPS = Karnofsky Performance Status. KPS score (in 10 unit increments).

Table 3. Multiple Logistic Regression Analyses for Single Nucleotide Polymorphisms in Cytokine Genes and the Occurrence of Palpitations in Women Prior to Breast Cancer Surgery (n = 301).

Predictor	Adjusted odds ratio	Standard error	95% CI	Z	p-Value
IL1B rs1143643	2.32	0.94	1.05, 5.12	2.08	.038
KPS score	0.97	0.01	0.95, 0.99	- 2.08	.037
Occurrence of back pain	2.07	0.76	1.01, 4.25	1.99	.047
Overall model fit: X^2 = 24.88; p = .0031; pseudo R^2 = .0954					
IL10 rs3024505	2.37	0.78	1.24, 4.52	2.62	.009
KPS score	0.97	0.01	0.94, 0.99	- 2.38	.017
Occurrence of backpain	2.13	0.78	1.04, 4.38	2.06	.040
Overall model fit: X^2 = 26.65; p = .0016; pseudo R^2 = .1022					
IL13 rs1295686	2.81	1.02	1.37, 5.74	2.83	.005
KPS score	0.97	0.01	0.94, 0.99	- 2.08	.037
Occurrence of back pain	2.15	0.79	1.04, 4.43	2.07	.038
Overall model fit: X^2 = 28.41; p = .0008; pseudo R^2 = .1089					

Note. Multiple logistic regression analyses of candidate gene associations with no palpitations versus palpitations. For each model, the first three principal components identified from the analysis of ancestry informative markers as well as self-report race/ethnicity were retained in all models to adjust for potential confounding due to race or ethnicity (data not shown). Predictors evaluated in each model included genotype (IL1B rs1143643: GG versus GA + AA; IL10 rs3024505: CC versus CT versus TT; IL13 rs1295686: GG versus GA + AA), KPS score (in 10 unit increments), and self-reported occurrence of back pain. Abbreviations. CI = confidence interval, IL = interleukin, KPS = Karnofsky Performance Status.

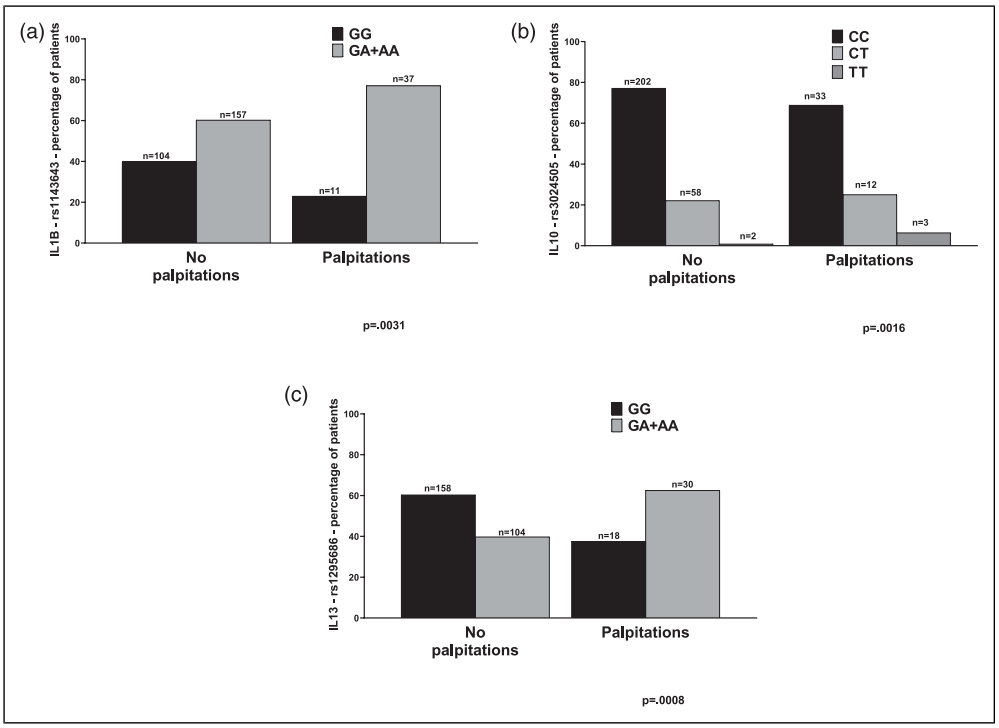

Figure 1. Differences between the no palpitations and palpitation groups in the percentages of patients who were homozygous for the common allele or heterozygous or homozygous for the rare allele for each significant polymorphism. Values are plotted as unadjusted proportions with corresponding p-values. A – Differences between the no palpitations and palpitation groups in the percentages of patients who were homozygous for the common allele (GG) or heterozygous or homozygous for the rare allele (GA+AA) for rs1143643 in interleukin (IL) 1-beta (IL1B). B – Differences between the no palpitations and palpitation groups in the percentages of patients who were homozygous for the common allele (CC), heterozygous for the rare allele (CT), or homozygous for the rare allele (TT) for rs3024505 in the IL10. C – Differences between the no palpitations and palpitation groups in the percentages of patients who were homozygous for the common allele (GG) or heterozygous or homozygous for the rare allele (GA+AA) for rs1295686 in IL13.

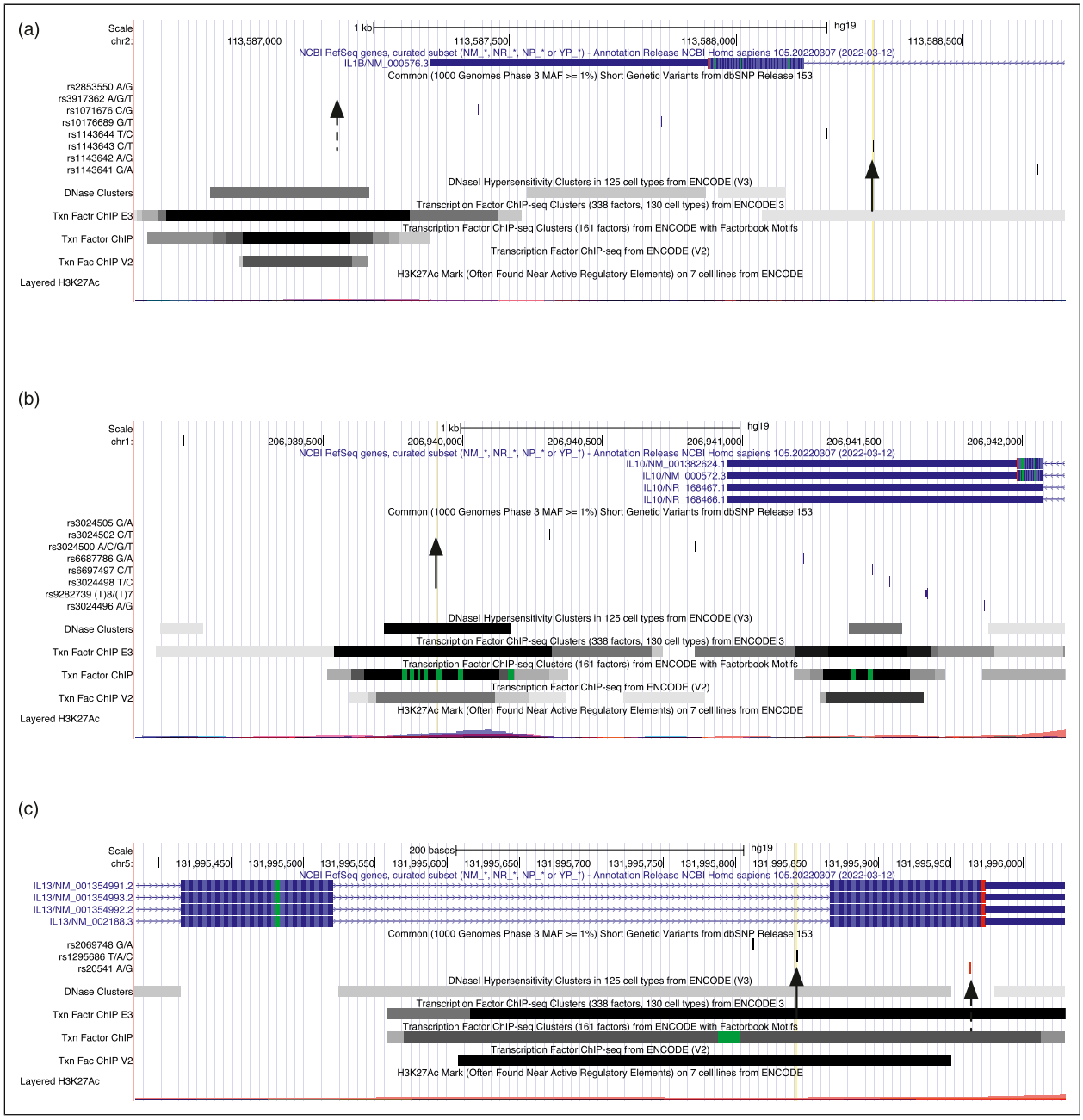

Figure 2. Visualization of the genomic regions flanking the single nucleotide polymorphisms (SNPs) in this study. Evaluation of these genomic regions for potential regulatory roles can provide overlapping sources of evidence for a regulatory region for the DNA and SNPs. The genomic regions are presented flanking (A) IL1B rs1143643, (B) IL10 rs3024505, and (C) IL13 rs1295686. Each track of the figure presents data in the assembly coordinate system. The gene models are provided by the "RefSeq" track to show the location of the genes on the assembly. The study SNPs are labeled and identified by a vertical line and solid arrow. SNPs in high linkage disequilibrium with study SNPS are identified with a dotted arrow. SNPs are annotated by dbSNP release 153. To evaluate the potential regulatory roles for these SNPs, putative regulatory regions are identified by the "ENCODE" tracks. The "DNaseI Cluster" track identifies regions that are DNase-I sensitive, a characteristic of promoter regions. The "Enhanced H3K27Ac" track identifies regions where modifications of histone proteins were found and are suggestive of enhancer regulatory activity. The "Txn Factor ChIP" track shows where transcription factors bind. Visualization is provided by the University of California Santa Cruz Human Genome Browser (Version hg19).

Each additional dose of the rare T allele was associated with a 2.37-fold increase in the odds of belonging to the palpitations group. For IL13 rs1295686 (G>A), a dominant model fit the data best. Carrying one or 2 doses of the rare A allele (GG vs. GA+AA) was associated with a 2.81-fold increase in the odds of belonging to the palpitations group.

Discussion

This exploratory study is the first to evaluate for associations between the occurrence of palpitations and variations in cytokine genes, their receptors, and regulators in women prior to breast cancer surgery. Differences in demographic and clinical characteristics between the 2 groups were discussed in detail in our previous publication (Sheng et al., 2022). Of note, functional status and back pain were the only 2 characteristics that remained significant in the multivariable model. No evidence was found for direct associations between these 2 characteristics and the occurrence of palpitations in oncology patients. However, in a study of women between the ages of 40 and 45 (Gold et al., 2000), higher rates of palpitations were associated with lower levels of physical activity. In addition, in 2 studies of healthy women, higher rates of palpitations were associated with greater activity impairment (Whiteley et al., 2013) and with lower physical component summary scores of the 36-item Short-Form Health Survey (Conde et al., 2006). Consistent with our a priori hypothesis, 3 SNPs in 3 different cytokine genes (i.e., IL1B, IL10, IL13) were associated with the occurrence of palpitations. These findings suggest that variations in genes involved in inflammatory processes may contribute to the occurrence of this symptom.

IL1B codes for a cytokine that is a mediator of various inflammatory processes including cell proliferation, differentiation, and apoptosis. The chronic inflammation associated with increases in IL1B contributes to the development of diabetes (Cano-Cano et al., 2022), metabolic syndrome (Silveira Rossi et al., 2022), atherosclerosis, sleep disturbance (Zielinski & Gibbons, 2022), and psychoneurological symptoms (e.g., depression, fatigue; Barandouzi et al., 2022).

In terms of IL1B rs1143643, that is located in an intronic region of chromosome 2, individuals who were heterozygous or homozygous for the rare "A" allele had a 2.32-fold increase in the odds of belonging to the palpitations group. While no studies have evaluated for an association between this SNP and palpitations, findings from a number of studies suggest that IL1B rs1143643 plays a role in post-traumatic stress disorder (Hovhannisyan et al., 2017), as well as in depression and responses to antidepressants (Baune et al., 2010; Draganov et al., 2019; Kovacs et al., 2016). In addition, it interacts with fatty acid molecules to modulate the odds of developing metabolic syndrome (Maintinguer Norde et al., 2018). Finally, IL1B rs1143643 is in high LD ($R^2 = 0.102$, D' = 1.0, $p < .0001$) with IL1B rs2853550, a SNP in a putative regulatory region (i.e., transcription factor binding; Figure 2(a)). Of note, IL1B rs2853550 is implicated in susceptibility for rheumatic heart disease (Muhamed et al., 2020), a condition that is often associated with atrial fibrillation and palpitations (Islam et al., 2013). Given the strong associations between IL1B and cardiac conditions and psychological problems that are included in the list of potential etiologies for palpitations in the general population and patients with breast cancer, additional research is warranted on the relative contribution of IL1B to the occurrence of palpitations.

Our findings suggest that increasing doses of the rare "T" allele of IL10 rs3024505, located downstream of the IL10 gene in a putative regulatory region (i.e., transcription factor binding; Figure 2(b)) increases the risk for palpitations. IL10 is a powerful anti-inflammatory cytokine that plays a role in stopping excessive activation of and auto-damage from the immune system. While no studies have found an association between this SNP and palpitations, it was linked to increased susceptibility for ulcerative colitis and Crohn's disease (Liu et al., 2022).

Highly relevant to our study is the fact that IL10 plays an important role in the development of cardiovascular diseases including atherosclerosis, cardiac fibrosis, hypertension, and cardiac hypertrophy (Xu et al., 2021). In addition, IL10 modulates insulin resistance (Iyer & Cheng, 2012) and is linked to an increased risk for atrial fibrillation in patients with metabolic syndrome (Rafaqat et al., 2021). Given that obesity and hypertension are 2 integral components of metabolic syndrome (Rafaqat et al., 2021) and that 40.0% of the women in the palpitations group reported a diagnosis of hypertension and 63.4% had a body mass index in the overweight (31.7%) or obese (31.7%) ranges, it is reasonable to hypothesize that some of these patients' reports of palpitations may be related to metabolic syndrome and/or associated cardiovascular disease. While detailed information on these patients' cardiovascular history is not available, this hypothesis can be evaluated in future prospective studies.

For IL13 rs1295686, located in the intronic region of the gene, individuals who were heterozygous or homozygous for the rare "A" allele (GG vs. GA + AA) had a 2.81-fold increase in the odds of belonging to the palpitations group. IL13 is a cytokine with broad functions that is widely expressed in most tissues (lung, heart, skin; Qian et al., 2021). IL13 encodes an immunoregulatory cytokine that is produced by Th2 cells and is involved in T cell and B cell maturation. It is best characterized for its role in the development of allergic asthma (Alsaffar & Alkholifi, 2022).

In terms of the specific SNP, IL13 rs1295868 has demonstrated an association with asthma (Halwani et al., 2018; Li et al., 2022). It is interesting to note that in 2 previous studies with the current sample, associations were found with this SNP and the occurrence of breast pain prior to surgery (McCann et al., 2012) and membership in a subgroup of patients with high levels of pain, fatigue, sleep disturbance, and depression (Doong et al., 2015).

While no data are available on associations between IL13 and palpitations, recent evidence suggests that this cytokine is associated with cardiovascular disease. Type 2 innate lymphoid cells (ILC2s) are a primary source of IL13. Under

physiologic conditions, heart ILC2s are maintained by self-renewal (Qian et al., 2021; Zlatanova et al., 2016). As noted in one review (Qian et al., 2021), while the signaling pathways and underlying mechanisms are not understood, IL13 is associated with cardiac fibrosis, cardiomyocyte proliferation, myocardial hypertrophy, and recruitment and differentiation of immune cells and chemokine secretion in the heart. In terms of a potential functional role addition, IL13 rs1295686 is located in a putative regulatory region (i.e., transcription factor binding sites; Figure 2(c)). In addition, this SNP is in high LD with IL13 rs20541 ($R^2 = 0.487$, D' = 0.982, $p < .0001$), which is a missense variant in the last exon of IL13 and is located in the same putative regulatory region. Both of these SNPs are associated with an increased risk for atopic dermatitis (Lee et al., 2020), a condition that is associated with an increased risk for atrial fibrillation. Similar to our other candidate gene findings, associations between palpitations and IL13 warrant additional investigation.

Limitations of this pilot study include the lack of detailed information on cardiac history; menopausal status; and characterization of palpitations (e.g., frequency, aggravating and relieving factors, impact). Given its cross-sectional design, future studies need to evaluate for changes in the occurrence and characteristics of palpitations, particularly as these women with breast cancer receive radiation therapy (Yan et al., 2022), adjuvant endocrine therapy (Choo et al., 2019; Kyvernitakis et al., 2014), and/or cardiotoxic chemotherapy (Croft et al., 2019; Essa & Lip, 2021; Essa et al., 2021).

Conclusions

While this pilot study is the first to identify associations between palpitations and 3 different cytokine genes, our findings warrant confirmation in a larger sample. Given the associations between inflammatory mechanisms and cardiovascular disease, as well as the increase in cardiac disease and associated complications in oncology patients (Kubota et al., 2021), additional research is warranted on this fundamental mechanism's role in the occurrence and severity of palpitation in patients with various types of cancer. This information could be used to identify women at increased risk for cardiac problems and to initiate additional diagnostic tests.

Author Contributions

Drs. Sheng, Carpenter, Smith, Paul, and Miaskowski contributed to the conception and design of the study and drafted the manuscript. All of the other authors contributed to the analysis and interpretation, critically revised the manuscript, gave final approval for the submission, and agree to be responsible for all aspects of the work and ensuring its integrity and accuracy.

Declaration of Conflicting Interests

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Supplemental Material

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